

RemarksAmendments

Claims 1, 8, 17, 26, and 28 have been amended to recite that a subset of the complexes are rod-shaped. Support for this recitation can be found in the specification at page 16, lines 1-3 : “DNA condensed with acetate and bicarbonate salts of CK30 polylysine assumed forms of long (100-300 nm) and narrow (10-20 nm) rods and relaxed toroids (~50-100 nm in diameter, 10-20 nm width)... ” Additional support can be found in Figures 10 and 13, which are electron micrograph pictures showing that the rod-shaped complexes are a subset of the total complexes.

Claims 1, 8, 17, 26, and 28 are amended to recite that the nucleic acid molecules of the rod-like complexes are condensed. Support for the condensed DNA in the complexes is found in Hanson<sup>1</sup>, col. 19, lines 60-64:

Condensed DNA is in a state in which interaction with the solvent is minimal and therefore the DNA is in the form of isolated spheres or toroids. It is not fibrous to an appreciable degree. Relaxed DNA, typically formed by dissociation of polycation from the DNA, forms fibers.

Rejection of Claims 1-5, 8-14, 17-19, 26, 28, 30, 31, 34, 35, 38-40, 51-55, 58-70, 73-82, 103, 104, 106-107, 114-115, and 122 Under 35 U.S.C. §112, First Paragraph

The claims stand rejected for failing to adequately support and enable a composition comprising only rod-shaped complexes. Claims 1, 8, 17, 26, and 28 have been amended to clarify that the complexes need not all be rod-shaped but rather that a subset of the complexes are rod-shaped. The claims, as amended, are commensurate in

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<sup>1</sup> Hanson is incorporated by reference in the subject application at page 9, lines 7-10.

scope with that which the Patent Office has held enabled: “Additionally, there is some support in the specification for compositions wherein the shapes of the complexes are a mixture of shapes, including spheres, toroids, relaxed toroids, toroids with tails, Y-shaped rods, small and large rods.” Office Action at page 4, emphasis added. Applicants respectfully request withdrawal of this ground of rejection.

The claims also stand rejected “for lack of enablement for compositions and methods of delivery to cells, wherein the intended use is for gene therapy applications.” Office Action at page 5. Applicants traverse this ground of rejection.

Previously, Applicants supplied Konstan *et al.*, (Human Gene Therapy, 2004 15:1255-1269) which teaches partial to complete reconstitution of Cystic Fibrosis Transmembrane Regulator (CFTR) function. Applicants submit herewith a declaration under Rule 132 of Dr. Mark J. Cooper, an inventor of the subject application and co-author of the Konstan publication. Dr. Cooper states that the successful restoration of CFTR function reported in the Konstan publication was achieved by preparing and administering compositions as taught in the specification as filed. See Declaration at paragraphs 3-7. Thus, the Konstan publication demonstrates that the teachings of the specification as filed are fully operative.

The Patent Office asserted that “this post-[filing date] art [Konstan] does not enable the instant invention.” Office Action at page 5. Applicants did not submit the Konstan publication to enable or supplement the disclosure of the instant application. Rather, applicants cited the Konstan publication to demonstrate that the compositions that they fully taught would function as they said they would. Applicants cited an after-filing date scientific publication to prove the truth and accuracy of their teachings. Such use of

after-filing date evidence is sanctioned in *In re Hogan and Banks*, 194 USPQ 527, 537 (CCPA 1977): “This court has approved use of later publications as evidence of the state of art *existing on the filing date* of an application.”

The *Hogan* court cites various situations in which such evidence can be used, including to show that a statement in the specification was inaccurate, citing *In re Marzocchi* 169 USPQ 367, 370 n.5 (CCPA 1971), or to show that the invention was inoperative or lacked utility, citing *In re Langer*, 183 USPQ 288, 297 (CCPA 1974). See *Hogan* at n. 17. Clearly if the U.S. Patent and Trademark Office can use after-filing date evidence to show that a statement made in a specification was inaccurate, then an applicant can use the same to show that a statement made in a specification was accurate. Clearly if the U.S. Patent and Trademark Office can use after-filing date evidence to show that an invention is inoperative or lacks utility, applicants can use the same to show that an invention is operative and has utility.

Thus applicants’ citation of an after-filing date publication and data to show the truth and accuracy of the specification’s assertions and to show that the invention is operative is perfectly correct and acceptable. The U.S. Patent and Trademark Office’s failure to accept such data constitutes legal error.

The specification is therefore enabled as filed for the full scope of the claimed subject matter. No undue experimentation would be required to practice the invention as claimed.

Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 1, 2, 8, 9, 11, 12, 17, 18, 26, 28, 30, 34, 38, 53, 65, 78, and 103 Under 35 U.S.C. §102(b)

Hanson (U.S. 5,844,107) is cited as anticipating the enumerated claims. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See M.P.E.P. § 2131.

Amended claims 1, 8, 17, 26, and 28 recite that the nucleic acid molecules in the rod-like complexes of the subject application are condensed. Condensed DNA does not form fibers, whereas relaxed DNA does:

Condensed DNA is in a state in which interaction with the solvent is minimal and therefore the DNA is in the form of isolated spheres or toroids. It is not fibrous to an appreciable degree. Relaxed DNA, typically formed by dissociation of polycation from the DNA, forms fibers.

Hanson, U.S. 5,844,107, col. 19, lines 60-64. Hanson teaches that fibers are formed when dissociation of polycation, caused by excess salt during the condensation reaction, prevents proper condensation of the complexes:

In Fig. 1F, we see a DNA complex, at a concentration of 1.068 M NaCl, which is above optimal for condensation for this complex. The DNA is in the relaxed state. Note the branched unimolecular toroids in which a nucleus of condensation is visible and the rod-like DNA fibers.

Hanson, U.S. 5,844,107, col. 6, lines 11-16.

The only rod-like structures Hanson teaches are fiber-containing complexes, which are not condensed as required by the claims. Hanson's fibers are formed by relaxed rather than condensed DNA. Hanson therefore does not teach the formation of

rod-shaped complexes of condensed nucleic acid. Accordingly, Hanson fails to teach all elements of the claims. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 3, 10, 19, 31, 35, 51-53, 63-65, 67,68, 76-78, and 104 Under 35 U.S.C. §103(a) over Hanson, Park, and Schacht

The Rejection of Claims 58-62, 66, 73-75, 79-82, and 122 Under 35 U.S.C. §103(a) over Hanson, Park, and Mao

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Hanson is the primary reference in each of these rejections. The deficiencies of Hanson with respect to the subject matter of claims 1, 2, 8, 9, 11,12, 17,18, 26, 28, 30, 34, 38, 53, 65, 78, and 103 are discussed above. Briefly, Hanson does not teach rod-shaped, condensed, nucleic acid complexes.

The secondary references are each cited to supply a teaching of a recitation in a dependent claim. Park is cited to teach PEGylated polylysine. Schacht is cited to teach attachment of PEG to polylysine via a cysteine residue. Mao is cited to teach lyophilization and rehydration prior to administration. None of these, however, teaches rod-shaped complexes that comprise condensed nucleic acids or how to achieve them. None of these therefore cures the deficiency of Hanson. The rejection fails because the combination of references fails to teach all elements of the claims.

Withdrawal of these rejections is respectfully requested.

The Rejection of Claims 4, 5, 13-14, 39, 40, 54, 55, 69, 70, 106, 107, 114, and 115 Under 35 U.S.C. §103(a) over Hanson, Park, Schacht, and Kwoh

Claims 4, 5, 13-14, 39, 40, 54, 55, 69, 70, 106, 107, 114, and 115 stand rejected as obvious in light of Hanson, Park, Schacht, and Kwoh. The rejected claims depend from independent claims 1, 8, 17, 26, and 28. Hanson is cited for teaching the subject matter of these claims. Hanson is discussed above. The secondary references are cited as teaching one or more recitations in a dependent claim. Park is cited as teaching PEGylated polylysine. Schacht is cited to teach attachment of PEG to polylysine via a cysteine residue. Kwoh is cited as teaching rod-shaped complexes of diameter less than 25 nm.

To establish a *prima facie* case of obviousness, three basic criteria can be met. First, there should be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there should be a reasonable expectation of success. Finally, the prior art reference (or references when combined) should teach or suggest all the claim limitations. M.P.E.P § 2143.

Here, the prior art provides no teaching to modify the complexes of Hanson to create condensed complexes having a rod-shape with a diameter of 10-20 nm as required by claims 1, 8, 17, 26, and 28.

Hanson's rod-like fibers form at high salt concentration:

In Fig. 1F, we see a DNA complex, at a concentration of 1.068 M NaCl, which is above optimal for condensation of this complex. The DNA is in the relaxed state. Note the branched unimolecular toroids in which a nucleus of condensation is visible and the rod-like DNA fibers.

Hanson U.S. 5,844,107, col. 6, line 12 and figure 1A. Kwoh's complexes, however, have a diameter greater than 25 nm at a salt concentration of 0.15 M NaCl. See Table 1 on page 178. Additionally, when Kwoh's polylysine complexes are conjugated to PEG, their diameter increases to 80.5 nm in water and increases even further in size to 187 nm in the presence of 0.15 M NaCl (see page 185, col. 1, line 12 to col. 2, line 3).

Thus, the skilled artisan could not combine the teachings of Kwoh and Hanson to make condensed complexes having a rod-shape with a diameter of 10-20 nm with a reasonable expectation of success because Hanson's teaching of rod-like fibers formed in high salt is incompatible with Kwoh's teaching of complexes having a diameter less than 25 nm only in low salt. Indeed, these different physical properties of the complexes taught by Kwoh and Hanson teach away from combining their teachings. Even if one of skill in the art were motivated to combine the teachings of Kwoh and Hanson, he would not know how to do so.

Nothing in Park or Schacht cures the art's failure to teach modification of Hansons' complexes with Kwoh's teachings because neither Park nor Schacht describe complexes having a diameter of 10-20 nm.

The Patent Office has failed to make a *prima facie* case of obviousness because the prior art contains no teaching of how to modify the complexes of Hanson to achieve the claimed compositions of claims 1, 8, 17, 26, and 28 with a reasonable expectation of success. Rejected claims 4, 5, 13-14, 39, 40, 54, 55, 69, 70, 106, 107, 114, and 115 depend from these claims; therefore, the prior art also fails to render obvious the subject matter of these claims.

Withdrawal of the rejection is respectfully requested.

Double Patenting Rejection

The Patent Office re-iterates a nonstatutory double-patenting rejection, citing Application No.'s 10/307,555 and 10/307,284. This rejection is improper.

Divisional applications resulting from a restriction requirement may not be used as a reference against the original application or other divisional application:

A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them.

35 U.S.C. § 121.



Application No.'s 10/307,555, 10/307,284, and the instant application are divisional applications of the same parent (Application No. 09/867,693) which was subject to a restriction requirement (October 2, 2002; copy attached as Exhibit 1). Thus, the applications cited by the Patent Office cannot be used as references against the instant application. The double-patenting rejection is therefore contrary to the statute. Applicants respectfully request withdrawal of the rejection.

All pending claims should thereafter be allowed.

Respectfully submitted,

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